ADDENDUM to SPONSOR'S EXECUTIVE SUMMARY

The following is a tabular summary of critical points of disagreement between FDA and MELA Sciences, arranged in a three-column table. The left column is the topic under consideration, the middle column contains a description of MELA Sciences' understanding of the position articulated by the FDA Review Team in their Executive Summary, and the third column is MELA Sciences' position.

This table was prepared after our review of FDA's Executive summary, which contained many points that directly contradict the legally binding Protocol Agreement that was executed in 2004 prior to the start of the pivotal trial.

The following topics are reviewed:

I. Instructions to the General & Plastic Surgery Devices Panel regarding the nature and scope of the Binding Protocol Agreement
II. 3-month follow-up group – F6 in Figure 4 of Protocol 20061
III. Protocol Agreement
IV. Physician Sensitivity
V. Intended Use
VI. Intended Use Population and Pivotal Trial Population
VII. Reader Studies
VIII. Identification of Atypical Lesions
IX. Statistical Methods
X. Benefit Risk
XI. Original Aim of the Study
XII. Lesion Classification Algorithm Development
XIII. Early Melanoma

The most fundamental areas of disagreement have to do with the legally Binding Protocol Agreement, signed in 2004 before the start of the pivotal trial, which provides, among other things, that:

a) Physician sensitivity cannot be measured on the pivotal study, therefore a target threshold of 95% lower confidence bound was established as the endpoint for MelaFind®;
b) The pivotal trial population of lesions represents the intended use population, that is, clinically atypical pigmented skin lesions;
c) Sensitivity and specificity as primary endpoints are appropriate metrics for evaluating the safety and effectiveness of MelaFind;
d) Histopathology is required for ground truth determination of sensitivity and specificity.

Other critical items include:

1. The intended role of the 3-month follow-up group and its significance to the study results in that group was neither intended nor included in any of the study's endoints and therefore, provides no insight into the sensitivity and specificity of MelaFind®. FDA Reviewers are under the impression that all lesions would be biopsied 3-months following the initial visit, however, this was only at the discretion of investigators, therefore, no expectation of histology could be assumed;
2. The value and validity of reader studies;
3. The intended use of MelaFind® proposed as the basis of study design and Protocol Agreement meetings with FDA beginning in 2004 has NOT changed substantively.

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TOPIC	**MELA Sciences' Understanding of FDA Position**	**MELA Sciences Position**
Instructions to General & Plastic Surgery Devices Panel Regarding the Nature and Scope of the Binding Protocol Agreement	The Protocol Agreement will evaluate MelaFind® performance, which is the evaluation of sensitivity and specificity. Sensitivity and specificity were recognized as appropriate metrics for evaluating safety and effectiveness, however, the protocol agreement was not designed to evaluate safety and effectiveness in clinical use.	1. The Protocol Agreement meetings conducted in 2004 centered on the following proposed intended use statement: ***MelaFind® creates multi-spectral digital dermoscopic images and performs and objective evaluation of the degree of disorganization of pigmented lesions of the skin. The system is intended as an aid to dermatologists in evaluating lesions that have one or more clinical and or historical characteristics of melanoma, but a final decision to biopsy has not yet been rendered.*** It is readily apparent that the clinical use of MelaFind® was anticipated from the very start in the design of the pivotal trial and Protocol Agreement discussions. Furthermore, the clinical use is embodied in Protocol Agreement Item 3: "The population (F3 and F4 in figure 4 on page 16) of lesions/patients that will be included in the primary analysis - i.e., lesions receiving clinical diagnoses of "Melanoma cannot be ruled-out" and "Not melanoma" - **are appropriate for evaluating the sensitivity and specificity of MelaFind when a final decision to biopsy has not been made by the study physician**." 2. Protocol Agreement Item 2 clearly states, "Sensitivity and specificity as primary endpoints are appropriate metrics for evaluating the safety and effectiveness of MelaFind®." Since the Protocol Agreement was discussed within the context of the targeted intended use statement, the safety and effectiveness to which Protocol Agreement Item 2 refers unequivocally refers to the ultimate clinical use of MelaFind®.
3-month follow-up group (F6 in Figure 4 of Protocol 20061)	1. Would provide information that is important to the evaluation of safety and effectiveness of MelaFind® for the intended use, that is, on lesions where the biopsy decision to rule-out melanoma has not been made. 2. Biopsies were to be performed on all lesions three months following the initial visit	1. At the time the follow-up group was designed some recent papers from Australia had suggested that short-term follow-up of atypical lesions might become a practice in the US by some dermatologists. The group was added in an attempt to capture these lesions, if the practice became established; 2. The follow-up group was designed to try to obtain information about whether there are any systematic differences in the types of clinically atypical lesions that are evaluated and determined not to require biopsy *versus* those that are biopsied. Figure 4 on p. 14 clearly shows that, contrary to the claim by FDA on p. 32, there was no intent to biopsy all lesions after 3 months (biopsy decisions were

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3-month follow-up group (F6 in Figure 4 of Protocol 20061) - continued		made by investigators based on medical reasons); 3. This was an optional group offered to investigators and was open to all investigators for the entire duration of the study. No patients were enrolled by any of the 23 investigators; 4. The pivotal trial inclusion criteria was biopsy *in toto* **OR** 3 month follow-up, therefore, there were no protocol deviations with respect to the 3 month follow-up group not being populated; 5. No accrual goals were established in the protocol for this group; no endpoints were tied to this group; 6. This group was not intended to evaluate MelaFind®'s performance on lesions not biopsied because without dermatopathology proof, assessment of diagnostic performance in this disease is not possible. This is the reason all of the primary and secondary aims were tied to biopsied lesions. Therefore, this group could NOT provide information important to the evaluation of safety and effectiveness of MelaFind®. Contrary to the statement by FDA (p. 32) comparison of "the MelaFind® result to the dermatologist's decision to defer immediate biopsy for a 3 month follow-up", would not "provide additional data to evaluate whether MelaFind® was able to effectively rule-out melanoma," in the absence of histological reference standard; 7. Even if any of the lesions initially enrolled in this group were biopsied at the follow-up visit, the statistical plan called for excluding these lesions from analyses of sensitivity and specificity, therefore, this group could not provide information important to the evaluation of safety and effectiveness of MelaFind®. Data were not to be used in even secondary endpoints; 8. This group was depicted as, and considered, "off study" in Figure 4 of the protocol, with light shading indicating that this group was not included in the main analyses as were F3 and F5 (and F2 for secondary endpoints); 9. Some of the kinds of lesions on the pivotal trial that might be followed short-term by the authors of the early papers were put in the "Melanoma Cannot be Ruled-Out, Unlikely Melanoma" group of the study, as explained by investigator Laura Ferris at April 27,

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		2010 meeting with FDA; 10. Biopsy at the 3-month follow-up visit for patients enrolled in this group was OPTIONAL, at the discretion of the investigator. Therefore, no expectation of histology from this group could be assumed.
Protocol Agreement	Violated by virtue of the fact that the optional 3-month follow-up group was not populated	1. Not violated because Protocol Agreement Item 3 (see Figure 4 of protocol 20061) states unambiguously that population F3 and F4 defines the intended use population; the protocol explicitly renders F6 (optional 3-month follow-up group) OFF STUDY, so, the intended use population is F3 and F5; 2. Binding and in full force. MELA Sciences invested 1 year (2004) to come to agreement with FDA on the appropriate study design to support the safety and effectiveness of MelaFind® prior to the start of the study. The protocol agreement was the direct sequitur to this effort with the agency to design the appropriate study. There were no deviations of the study with respect to the optional 3-month follow-up group – it was open from start to finish for investigators to enroll patients, if they so desired.
Physician Sensitivity	Direct comparison of physician false negatives and MelaFind® false negatives on the pivotal trial is an acceptable means to quantify the relative sensitivity of MelaFind® and investigators	1. Sensitivity of physicians cannot be measured on the pivotal study because only biopsied lesions could be enrolled in order to calculate sensitivity and specificity – Protocol Agreement Item 5 requires histopathology to establish ground truth for sensitivity and specificity calculations; 2. **On the pivotal trial, it would be impossible to enroll melanomas that were missed by physicians since missed melanomas would not be biopsied.** Because of this reason, a threshold level of success for MelaFind® sensitivity (≥ 95% at > 95% lower confidence bound) was selected – the historical control for this was the Bataille paper demonstrating the highest reported measured sensitivity in the literature of 94% (this was covered in Protocol Agreement Item 4b); 3. The bulk of the literature demonstrates physician biopsy sensitivity to be 70-80% for early melanoma; 4. Physician sensitivity relative to MelaFind® can be estimated in reader studies, which was the intent of the companion Reader Study

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		(Protocol 20063).
Intended Use	Intended use has changed from lesions "suspicious" of melanoma to all atypical lesions	1. Intended Use statement in Protocol 20061 (pp. 13): ***"The system is intended as an aid to dermatologists in evaluating lesions that have one or more clinical or historical characteristics of melanoma, but a final decision to biopsy has not yet been rendered.*** ***The purpose of this clinical trial is to demonstrate that MelaFind®, a new instrument that uses machine vision FOR NON-INVASIVE EARLY DETECTION OF CUTANEOUS PIGMENTED MELANOMA, is safe and effective."*** 2. Intended use statement has not changed, rather, it has always been for lesions that are "atypical for suspicion of melanoma" (see Figure 4: Population Schema from pivotal trial), **which defines a universe of atypical lesions that have one or more clinical or historical characteristics of melanoma** (as opposed to atypical for suspicion of psoriasis or atopic dermatitis, for example). 3. "Clinically atypical pigmented skin lesions for which a final decision to biopsy to rule-out melanoma has not been made by the physician" has always been the group of lesions for which MelaFind® was designed to provide information to assist in the detection of melanoma. 4. Lesions "atypical for suspicion of melanoma" are evaluated by physicians to determine whether they are, indeed, "suspicious"; if an atypical lesion is suspicious, it is biopsied. Not all lesions that are "atypical for suspicion of melanoma" are "suspicious"; we believe that this basic point may be the root of the disagreement with FDA. Furthermore, a lesion that is "suspicious" to one physician may be "not suspicious" to another physician, as should be obvious to anyone practicing dermatology and as demonstrated in the reader study (20063). 5. The pivotal trial enrolled 87 lesions with only **ONE** characteristic of melanoma; four were melanomas. Three of these melanomas were identified only as "ugly ducklings." MelaFind® provided positive results for all four of the melanomas with only 1 clinical or historical

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		characteristic of melanoma.
Intended Use Population and Pivotal Trial Population	1. Prior to the start of the pivotal study, and codified in the Protocol Agreement, the exclusion of "F2 - definite melanoma" group results in a population of lesions for which the investigators had not made a **final** decision to biopsy, thereby, directly representing the intended use population. During the review of the PMA, several new reviewers at FDA took the position that the appropriate intended use population is atypical pigmented lesions NOT enrolled in the pivotal study, since all lesions on pivotal trial were biopsied. 2. Depending on the expertise level of the examining dermatologist of Protocol 20061, it is possible that a number of atypical lesions may not have been included in the study if the investigators in Protocol 20061 represent an upper level of expertise.	1. As per Protocol Agreement Item 3, lesions on the pivotal trial, when group F2 ("definite melanoma") are excluded, represent lesions for which the investigator had not made a **final** decision to biopsy; 2. Protocol Agreement Item 3 was worded with the agency to precisely track the language of the proposed intended use – "to assist in the evaluation of pigmented skin lesions having one or more clinical or historical characteristics of melanoma before a final decision to biopsy has been rendered"; 3. Since different physicians select different atypical pigmented skin lesions to biopsy, lesions on the pivotal trial that were biopsied by one investigator would not necessarily be biopsied by either other investigators on the pivotal trial or many other physicians in the intended use setting; 4. Low kappa score (0.29) in the Companion Definitive Reader study confirms the inter-observer variability in the selection of suspicious (requiring biopsy) lesions from a group of atypical lesions. 5. The wide range of specificities of individual investigators in Protocol 20061 suggests that their level of expertise was also highly variable, thus lesions from investigators at all levels of expertise were included in the study.
Reader Studies	1. Reader studies have limited value because pictures of lesions are used, as opposed to actual face-to-face evaluation. 2. Proper evaluation of lesions requires a detailed patient history including personal and family history of atypical pigmented lesions or melanoma as well as a full examination of the patient and including a global view of pigmented lesions and their pattern.	1. Reader studies have been validated in the dermatologic and radiologic literature as means of assessing physician performance for the detection of skin cancer, colon cancer, lung cancer, and breast cancer; 2. Reader studies are the foundation for teledermatology and teledermoscopy, which have been validated in the literature, and are being used extensively by the US military and in rural settings, and are increasingly being used in suburban settings; 3. Lesion photographs are used to train dermatologists, dermatology residents, and dermoscopists; 4. Reader Studies conducted by MELA Sciences (Protocols 20081 and 20063) included 3 high resolution images from standard cameras: 21 inches away (overview, providing a global view of the patient's

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		skin), 8 inches away (close-up), and dermoscopic 5. Included extensive clinical information – such as personal and family history of melanoma, dysplastic nevi, and non-melanoma skin cancer, and physical examination findings. Doctors involved in these reader studies often reported having MORE information about the patient and lesion than in face-to-face settings; 6. The companion Definitive Reader Study demonstrated physician biopsy sensitivity of just 72% compared to MelaFind® 97% ($p < 0.0001$) with a kappa score of 0.29 (fair agreement) indicating great heterogeneity in the biopsy decision by physicians.
Identification of Atypical Lesions	Only board certified dermatologists can do this since only Board certified dermatologists were in the pivotal study. No training methods for other physicians have been evaluated by the sponsor in clinical studies.	1. Two PA's (physicians assistants) served as investigators on the pivotal trial, and enrolled patients; 2. Physicians of many different specialties and patients have been, and are, readily taught to identify atypical lesions. The difficulty is in the evaluation of atypical pigmented lesions to determine those that are suspicious, thereby requiring biopsy. Dermatologists have unique training and qualifications in the **evaluation** of atypical pigmented skin lesions, however, the identification of atypical pigmented skin lesions is performed routinely by physicians of many specialties as well as patients and other clinicians (nurses, physicians assistants, etc.); 3. MelaFind® is to be used on clinical atypical pigmented skin lesions, that is, those having one or more clinical or historical characteristics of melanoma, such as asymmetry, border irregularity, color variegation, diameter greater than 6 mm, evolving, patient concern, regression, and "ugly duckling." Educational and promotional campaigns will necessarily teach physicians and patients the meaning of these terms. Many groups – dermatologic associations, patient advocacy groups, health and beauty magazines, and universities – have provided effective tools and programs that we will model. 4. The final intended use statement that was submitted to FDA and used as the basis of the Protocol Agreement discussions did not limit the use of MelaFind® to any physician group, as directed by the then Director of the Review Division, Dr. Celia Witten.

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Statistical Methods	The protocol specified that exact binomial methods would be used. Clopper-Pearson, Score, and mid-P methods all show significant or borderline significant results for sensitivity being greater than 95%, using a one-sided test.	1. As per Protocol 20061, which specified that an exact binomial method would be employed, and in accordance with our statistical plan, MELA Sciences employed the mid-P exact binomial method since this is the preferred method of analysis when evaluating data at the extremes of a distribution. All sensitivity endpoints were met; 2. The Casella-Blith-Still correction to the Clopper-Pearson approach, which accounts for the over-conservative nature of Clopper-Pearson at the extremes of the distribution, also demonstrates that all sensitivity endpoints were met.
Benefit Risk	The fatal risk of missing melanomas (two of 127) is not worth the marginal benefit of a clinically meaningless reduction in biopsy ratio compared to dermatologists	1. The position of the agency is completely without context. Two of 127 is less than 2% whereas the literature establishes that dermatologists routinely miss between 10-30% of melanomas. Sensitivity of at least 95% was set as MelaFind®'s endpoint because clinician sensitivity could not be measured on the pivotal trial. (See comments above on physician sensitivity); 2. The Protocol Agreement specifies that the endpoint for MelaFind® sensitivity is an absolute threshold for MelaFind® of at least 95%, and the endpoint for MelaFind® specificity is superiority ($p < 0.05$) *versus* investigators. This is the case because investigator sensitivity cannot be measured, but investigator specificity and MelaFind® sensitivity and specificity can be measured. It follows, then, that analyses of relative false positive or true negative results of MelaFind® and investigators is appropriate in the context of benefit risk, however analyses of relative true positives and false negatives is NOT appropriate in the context of benefit risk because investigator true positive and false negative results cannot be obtained on the pivotal trial; 3. MelaFind® met the endpoints of the study – sensitivity greater than 95% (lower confidence bound) with higher specificity than dermatologists (9.9% versus 3.7%, $p = 0.02$). The literature and companion Definitive Reader Study demonstrate the dermatologist sensitivity for early melanoma is in the 70-80% range. Therefore, the main message of the MelaFind® pivotal study is that very high sensitivity (over 98%) can be achieved with no greater risk from biopsy of non-melanomas, by virtue of its higher specificity than

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		dermatologists, which translated into a marginally lower biopsy ratio (7.6:1 to 7.9:1). The main benefit is NOT biopsy reduction, rather very high sensitivity to early melanoma without increased risk of biopsies of benign lesions.
Original Aim of the Study	MelaFind® for the reduction of unnecessary biopsies	1. Intended Use in Pivotal Trial Protocol 20061 (pp. 13): **The system is intended as an aid to dermatologists in evaluating lesions that have ONE OR MORE CLINICAL OR HISTORICAL CHARACTERISTICS OF MELANOMA, but a final decision to biopsy has not yet been rendered.** The purpose of this clinical trial is to demonstrate that MelaFind®, a new instrument that uses machine vision **FOR NON-INVASIVE EARLY DETECTION OF CUTANEOUS PIGMENTED MELANOMA, is safe and effective.** **2.** Also, per Protocol Agreement Item 4a: "The sample size -93 dermatohistopathologically-confirmed melanomas among lesions receiving dermatological diagnoses of either "Melanoma cannot be ruled out" or "Not melanoma", with a minimum total number of lesions of 1200 – **is sufficient for evaluating the sensitivity and specificity of MelaFind® to correctly identify malignant melanoma."** 3. The original aim of the study was to prove that MelaFind® can safely detect melanomas at a very high absolute threshold of sensitivity (> 95%) without a corresponding decrease in specificity relative to investigators. High sensitivity often comes at the cost of decreased specificity. The clinically meaningful outcome is one where the increase in sensitivity (from that which is seen in the literature) is achieved without the added morbidity of additional biopsies. This is the reason that sensitivity and specificity were CO-PRIMARY ENDPOINTS. 4. Furthermore, if the original claim were simply to reduce biopsies of suspicious lesions, Protocol Agreement Item 3 would be superfluous: *The population (F3 and F4 in figure 4 on page 16) of lesions/patients that will be included in the primary analysis - i.e., lesions receiving clinical diagnoses of "Melanoma cannot be ruled-out" and "Not melanoma"* - ***are appropriate for evaluating the***

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		sensitivity and specificity of MelaFind® when a final decision to biopsy has not been made by the study physician. There would be no need to define a group (as Protocol Agreement item 3 defined) where the decision to biopsy had not yet been rendered if the intended use were for the evaluation of atypical pigmented lesions to rule-out (or prevent) biopsy (i.e., after the final decision to biopsy has been made). In fact, lesions undergoing biopsy as definite "Melanoma" (F2 population) were explicitly excluded from the primary endpoints in order NOT to prevent biopsies of melanomas.
Lesion Classification Algorithm Development	MelaFind®'s positive detection algorithm was changed in Protocol 20031 to increase sensitivity for Protocol 20061	1. Protocol Agreement Item 9 stipulates that "The classifier will be fixed prior to analysis of the data from Protocol 20031" 2. This was the entire reason the Sponsor required a Data Custodian to sequester the images and CRF data. Sponsor did not stop development of its lesion classification algorithm until well after study closure, as permitted by the Agency, and discussed throughout the Protocol Agreement meetings. The Sponsor had no final classifier prior to 2008.
Early Melanoma	Sponsor defines early melanoma as non-ulcerated, not bleeding and less the 2.2cm	1. Sponsor uses "e.g., non-ulcerated, not bleeding, or less than 2.2 cm)" as examples of prospective criteria that could be used to provide reasonable certainty that MelaFind® is not applied to advanced melanomas. This was at the Agency's request in meetings that occurred in August and September, 2010, and was based on the inclusion/exclusion criteria of the pivotal trial. Sponsor feels that limiting the use of MelaFind® to clinically atypical lesions that do not fit any of the listed contraindications for use is appropriate for defining the population of lesions suitable for analysis with MelaFind® for the detection of early melanoma, as has been shown in the data. The application of these criteria resulted in 125 of the 127 melanomas on the pivotal trail meeting NIH's criteria for "early melanoma."